REMARKS/ARGUMENTS

Consideration of this Preliminary Amendment is respectfully requested. Claims 35, 37-38, 39-51, 53-56 and 58 remain in the application.

Applicants have amended the claims to address each of the issues raised by the Examiner in the Office Action of October 16, 2003. It is believed that the claims are in condition for allowance. The Applicants response to each of the rejections is set forth below.

Request for Interference

As will be shown hereafter, at least some of the claims in this application are allowable. Applicants have previously requested that an interference be declared between the claims of this application and United States Patent No. 6,340,369 to Ferree. It is again requested that the claims of this application be put into interference with United States Patent No. 6,340,369 to Ferree, for the reasons previously requested.

Claims Rejections under 35 U.S.C. § 112, ¶1

1. Claims 35 & 37-38 are rejected under 35 U.S.C.§ 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner states: "No proper antecedent basis nor conception in context with that described within the specification at the time of filing the instant invention is apparent for treating human disc diseases using 'a carrier in the form of a hydrogel... forming a three-dimensional carrier' (i.e., as it relates to claim 35)." *Office Action dated October 16, 2003 at page 3.*

Although applicants do not agree with the Examiner's interpretation of the claims in view of the specification, Claim 35 has been amended to delete "in the form of a hydrogel". . . "forming a three-dimensional carrier." It is therefore respectfully submitted that the amendment to Claim 35 overcomes this rejection.

2. Claims 35, 37-51 & 53-58 are rejected under 35 U.S.C. § 112, first paragraph, for the following reason:

> the specification, while being enabling for using therapeutic compositions comprising "early childhood" human intervertebral disc cells and a carrier that contain required and defined cell stimulants/growth factors/carrier molecules to aid in the treatment of human disc diseases or injuries, does not reasonably provide enablement for uses of such cells from adolescents or adults wherein annulus and/or nucleus cells no longer exist, or for compositions missing required/defined components or comprising carrier derivatives thereof (i.e., in that none of the claims recite each and every required component, and instead claim piecemeal recitations).
>
> The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the reasons made of record in Paper Nos: 3 (mailed 9/13/00, 7 (mailed 5/09/01) and 16 (mailed 5/21/02) of old claims 35-38, etc.
>
> It is noted that Applicant's' arguments on pages 6-7 of the response, as it relates to the claims now being "revised... to a method" fails to address the issues raised in the previous Office actions. Additionally, the Declaration filed 7/26/01 fails to address the issues for these new claims. It is noted that Declarant's "opinion" that the results of the "sand rat" model is "translatable to human" is not fully persuasive for methods of treatment, because the "sand rat" is a quadruped that would not reasonably experience the shock absorber function/stress/ mechanical loading requirements of the disc in the larger biped human, in order to provide a reasonable enabling treatment, based on the teachings of Aigner et al. (1997), Guilak et al. (1999), Frick et al. (1994) and Luk et al (1997) previously made of record. *Office Action dated October 16, 2003 at pages 3-3.*

The Examiner's reasons for this rejection have been carefully reviewed. It is noted that "with regard to cell types to be implanted" the Examiner states: "it is well recognized in the art that annulus cells and nucleus cells have distinct morphologic, phenotypic and functional properties." In fact, Chelberg, *et al.* state that the disc is comprised of 2 distinct regions, the nucleus pulposus and the annulus fibrosus. (Page 43). The Examiner raises the Guilak et al, (199), the Aignor et al. (1997), Frick et al. (1994) and Luk et al. (1997) articles.

The Examiner states:

> In view of the teachings of Aigner *et al.* and Guilak *et al.*, that intervertebral disc tissue comprises a heterogeneous population of cells, which have distinct biosynthetic capacities, and which respond to stimuli

> differently, and the lack of disclosure in the instant application with regard to which intervertebral disc cells to isolate, expand and use in a method of treating intervertebral disc disease, and further in view of the lack of prior art data which teaches implantation of a particular expanded population of disc cells, it would have required undue experimentation for one of skill in the art to provide an expanded population of the appropriate intervertebral disc cell type and use the expanded population in a method for treating disc disease by implanting the cells into intervertebral disc tissue. *Office Action (Paper #3) dated 9/13/00 page 5.*

The purpose of the experiments in the Aignor, *et al.* article was to examine the distribution and expression of type X collagen which is a marker of hypertrophic chondrocytes and though to be involved in cartilage calcification in human discs. The study found for the first time that type X collagen is a possible gene product of the intervertebral disc cells and a potential biochemical component of the disc matrix. (See abstract). In the background of the article Aignor, *et al.* state: "The intervertebral disc consists of three distinct regions; the outer firm annulus fibrosus, the inner soft pulpy nucleus pulposus, and the hyaline cartilage-like endplate interspersed between the rest of the disc and the vertebral bodies." (P 263). Aignor, *et al.* then state: "However, the organization and composition of these regions differ markedly." (P 263) The fact that cells differ in the amount and density of collagen does not mean the cells can't be reproduced and used to treat a diseased or injured invertebral disc. Aignor, *et al.* have nothing whatsoever to do with treating diseased or injured invertebral discs. Aignor, *et al.* certainly does not stand for any proposition that undue experimentation is required to carry out the claimed invention.

Guilak, *et al.* discuss a study to quantify the mechanical properties of living cells of porcine intervertebral disc. The results of the study were that intervertebral disc cells exhibited viscoelastic solid behaviors and the scientists concluded that there was new evidence for the existence of two biomechanically distinct cell populations in the intervertebral disc. (See abstract). The results of the study were that there exists two biomechanically distinct cell populations in the intervertebral disc. The fact that spatial difference exist in the morphology and phenotype of these cells between regions corresponding to the annulus fibrosis and nucleus pulposus, does not mean the cells can't be reproduced and used to treat a diseased or injured

invertebral disc. Guilak, *et al.* have nothing whatsoever to do with treating diseased or injured invertebral discs. The Guilak, *et al.* article certainly does not stand for any proposition that undue experimentation is required to carry out the claimed invention.

Next, the Examiner stated:

> With regard to the state of the art of implanting intervertebral disc "tissue" to a site requiring such implantation, both Frick *et al.* and Luk *et al.* teach grafting of intervertebral disc tissue into animal models. Both Frick *et al.* and Luk *et al.* clearly indicate that while different animal models may be suitable for initial studies on intervertebral disc properties as well as for studying the effects of different therapeutic regimens for treating disc diseases, one cannot extrapolate results from these animal modes to human. Moreover, Luk *et al.* indicate that while there is a suggestion that after an initial period of degeneration the disc becomes stabilized and may be even be able to regenerate, the extent and the effectiveness of the regenerative process is still unclear and will need further studies. Thus, the state of the art is such that grafting intervertebral disc tissue for the purpose of treating disc disease is neither routine nor predictable. Given the lack of sufficient guidance in the specification and the state of the art, it would have required undue experimentation for one of skill in the art to practice the method as claimed. As the methods of treating disc disease are not enabled, the therapeutic compositions comprising in vitro expanded intervertebral disc cells are not enabled a swell. (emphasis added). *Office Action (Paper #3) dated 9/13/00.*

Luk, *et al.* "explored the possibility of intervertebral disc autografting in a bipedal animal model by isolating a lumber disc together with the adjacent end plates and repositioning it with minimal internal fixation." (See abstract). The results suggested that a fresh intervertebral disc autograft could survive a period of ischemia", *i.e.*, the experiments worked. (See abstract). Lu, *et al.* do not stand for the proposition that the state of the art is such that grafting intervertebral disc tissue for the purpose of treating disc disease is neither routine or predictable. Luk, *et al.* simply stated that further studies are required to validate the results that they found. Luk, *et al.* certainly do not stand for any proposition that undue experimentation is required to carry out the claimed invention.

Lastly, the Frick, *et al.* article is a study of disc transplantation. Frick, *et al.* do not deal at all with disc culture or autologous disc cell implantation. Thus, it is not relevant to the claims in this patent application. Disc transplantation as preformed by Frick, *et al.* did not work as shown

in the publication; hence, the cell-based approach described in this patent application was developed.

When determining whether undue experimentation is needed one must consider what the claims require. While some experimentation may be desirable or even necessary the law certainly provides for such latitude. There is sufficient guidance in the specification such that undue experimentation for one skilled in the art is not required to perform the methods claimed. It is therefore respectfully submitted that the methods of treating disc disease meet the enablement requirements of 35 U.S.C. §112, ¶1

3. Claims 43, 50 and 58 are rejected under 35 U.S.C. § 112, first paragraph, for the following reason:

> the metes and bounds of what cell stimulants "growth factors or cytokines", and carrier "derivatives" thereof in new claims 43, 50 and 58, are required to proliferate the "cultured disc tissue", etc. are not adequately defined in the specification, nor specifically defined in the claims; thereby preventing the skilled artisan from knowing how to determine how to make and use these "cultured disc tissue" without requiring undue experimentation to determine such (i.e., as it relates to claims 43-44, 50-51, 55 & 58). *Office Action dated October 16, 2003 at page 3.*

Claims 43, 50 and 58 have been amended to delete the term "collagen derivatives". In addition, Claims 44, 51 and 55 have been amended to limit the claims to "fetal calf serum" and fetal bovine serum". Support for this amendment may be found on page 5 of the specification. Lastly, the Examiner's attention is directed to Claims 45 and 56 that have been amended to be limited to the specific materials disclosed in the specification, see also page 5. It is therefore respectfully submitted that this rejection has been overcome.

In summary, the Examiner has set forth 3 rejections under section 112, 1st paragraph. The Applicants have amended the claims so as to overcome the 1st and 3rd rejections. Regarding the second rejection, the articles cited simply do not stand for the proposition that undue experimentation is required to perform the claimed invention.

Claims Rejections under 35 U.S.C. § 112, ¶2

Claims 37-52, 54 & 58 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. It is confusing why it is important to "treat... a diseased or injured invertebral (sic) disc having nucleus and annulus regions", when the disease or injury (or even normal development) may have destroyed these two regions which are normally present in healthy early childhood tissue (i.e., as it relates to claim 39).

There are several reasons why Claim 39 includes "treating a diseased or injured invertebral disc having nucleus and annulus regions." First, is to claim all the Applicants have a right to claim – note the distinction from, for example Claim 53. Use of this language is, of course, supported by the Applicants specification. Such a distinction is not confusing to those skilled in the art. Specifically, note that Chelberg, *et al.* discusses such distinction. Quite obviously, if one of these two regions was destroyed, then healthy tissue would be taken for a healthy location for culturing. Second, the claims of United States patent No. 6,340,369 to Ferree – which the Applicants are entitled to have determined by an interference – uses that terminology. Notably, the Examiner has not stated why use of that questioned term is indefinite. Applicants submit that the term is not indefinite.

2. It is further confusing why one would "mince" "intervertebral cells", verse "disc tissue" as disclosed on page 5 of the specification (i.e., as it relates to claims 41 and 54).

Claims 41 and 54 have been amended to clarify that the – disc tissue – is minced. With this clarification, the rejection for indefiniteness has been overcome.

3. No antecedent basis exists in claims 37 & 38 for the recitation of "therapeutic composition" in base claim 35, which is now directed to "a method".

Claims 37 and 38 have been amended to provide proper antecedent basis. This rejection is now moot.

4. No antecedent basis exists for the recitation of "said cultured disc tissue" in claims 39 & 52, or for "said cultured human intervertebral disc tissue" (i.e., as it relates to claims 42 & 49) and

Claims 39 and 52 have been amend to provide appropriate antecedent basis. This rejection is now moot.

5. No antecedent basis exists for the recitation of "obtain an explant" in base claim 39 (i.e., as it relates to claims 41, 45, 47 and 51).

Antecedent basis is present in Claims 41, as amended. The "explant" is the object of the mincing steps. It is not part of Claim 39. Therefore, there is antecedent basis for term "obtain an explant" in Claims 44, 45, 47, and 51.

6. No antecedent basis further exists for the recitations of "said isolated disc tissue" or "said distributed tissue" in claim 47.

Claim 47 has been amended to provide proper antecedent basis.

7. Claims 35, 37-38 & 47-51 are rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

> The omitted steps are: "debriding the diseased or injured disc tissue" in order to have room to implant a "three dimensional structure", as required in claims 35 & 47.
>
> It is noted that Applicants are attempting to alter a previous product-by-process claim into a treatment claim, which contains limitations that do not readily flow into a method of treatment, as currently claimed (i.e., as it relates especially to claims 35 & 47). *Office Action dated October 16, 2003 at pages 5-6.*

It is acknowledged that MPEP § 2172.01 states, *inter alia*:

> A claim which omits matter disclosed to be essential to the invention as described in the specification or in other statements of record may be rejected under 35 U.S.C. 112, first paragraph, as not enabling.

That section of the Manual is not applicable to the present claims. The invention does not require "debriding". More specifically, the specification states:

> The implantation of in vitro propagated human disc cells, preferably in an implantation carrier, can be performed by any suitable procedures know in the art. For example, where debridement of the defect disc tissue is not required, the disc cells embedded in, e.g., an injectible hydrogel can be injected in the desired area of the intervertebral disc of the patient without invasive surgical procedures. However, very often, it is desirable to remove the diseased disc tissue before the implantation of the *in vitro* cultured disc cells. In that event, the diseased disc tissue can be surgically removed creating a cavity or void, and *in vitro* cultured human disc cells, preferably autologous disc cells, in an implantation carrier are implanted in the removed area.
>
> Surgical techinques for removing diseased disc tissues and for surgically implanting a three-dimensional construct in human intervertebral discs are known in the art and can all be used in the present invention. (emphasis added) *Specification page 9, line 24 – page 10, line 4.*

Clearly, the "debriding" step is optional. This rejection should be withdrawn.

In summary, the Applicants have addressed each of the 7 rejections under Section 112, second paragraph and believe that each of them have been overcome. It is therefore requested that this rejection be withdrawn.

Claim Rejection under 35 U.S.C. § 102(a)

Claims 52-58 are rejected under 35 U.S.C. § 102(a) as being anticipated by Chelberg *et al.*, for the reasons made of record in Paper No. 3 & 16 for old claims 35-38, and as follows.

> It is noted that Applicants' arguments on pages 7-8 of the response, as it relates to "in view of the amendments to the Claim 35" fail to address the issues raised in the previous Office actions, as it relates to these product claims and method of producing such, which Chelberg et al reasonably teach for the reasons previously made of record.
>
> The issue again then becomes that if the product in a product-by-process claim (i.e., a "cultured disc tissue" comprising a carrier material and in vitro "live" human intervertebral cells) is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior art product was made by a different process. *In re Thorpe*, 227 USPQ 964, 944 (Fed. Cir. 1985); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983). *Office Action dated October 16, 2003 at page 6.*

In paper #3 the Examiner stated:

> Chelberg *et al.* disclose a method of growing human annulus and nucleus cells obtained from adult human intervertebral discs comprising isolating cells form the tissue, casting cells in alginate microspheres in the presence of a CaCl2 solution, and incubating the cells in culture dishes in the presence of fetal bovine serum at 37°C (see, e.g., pages 44-45 under "Tissue Processing"). The cells express a differentiated phenotype, i.e., the cells synthesize glysaminoglycans, Type I and Type II collagens, aggrecan, and other proteoglycans (see, e.g., pages 48, rights hand column, through page 50, left column). As there is no distinction between the cells of Chelberg *et al.* and the cells of the instant invention, the reference of Chelberg *et al.* anticipates the claimed invention. *Office Action (Paper #3) dated 9/13/00 at pages 8-9.*

Claim 52 has been cancelled. Claim 53 has been amended to include the limitation of claim 57 – that the cultured disc tissue is combined with a carrier material.

The Chelberg et al. article details a study demonstrating the phenotypes of disc cells of healthy, human non-degenerative intervertebral discs. Chelberg et al. take adult human intervertebral discs from donor who had no spinal pathology or chronic debilitating illness. The cells were isolated from human annulus and nucleus. The nucleus pulposus and annulus fibrous regions were each minced with a scalpel. The cells were digested in fetal bovine serum and cast in alginate microspheres. *Pages 44-45.* No carrier was present. No growth factors were present.

When tested for cell yield "there was no indication of cellular division with either annulus or nucleus cells. *Page 48, right column.* The summary of the Chelberg et al article shows that cells of the nucleus pulposus and annulus fibrosus exist as several heterogeneous populations in terms of extracellular matrix production, glycosaminoglycan synthesis, and collagen production." *Page 51.*

Quite clearly, Chelberg *et al.* does not anticipate or make obvious Claims 53 – 56 and 58 as presently amended.

Summary

Enablement. The Examiner has set forth 3 rejections under section 112, 1st paragraph. The Applicants have amended the claims so as to overcome the 1st and 3rd rejections. Regarding the second rejection, the articles cited simply do not stand for the proposition that undue experimentation is required to perform the claimed invention.

Indefiniteness. the Applicants have addressed each of the 7 rejections on indefiniteness and have either amend the claims to obviate the rejection or explained why such rejection is incorrect.

Prior art rejection. The rejection of Claims 52-56 and 58 as being anticipated by Chelberg *et al.* has been addressed and those claims amend to distinguish the cited reference.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450, on February 11, 2004.

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